We could predict good responders to vagus nerve stimulation: a surrogate marker by slow cortical potential shift(Abstract_要旨)

AUTHOR(S):

Borgil, Bayasgalan

京都大学	博士（医学）	氏　名	Bayasgalan Borgil
論文題目	We could predict good responders to vagus nerve stimulation: a surrogate marker by slow cortical potential shift （脳波の緩電位変化は迷走神経刺激療法の治療効果の代替マーカーとなる）		

（論文内容の要旨）

Objective: Vagus nerve stimulation (VNS) is a palliative treatment option for patients with intractable epilepsy who are not good candidates for surgical resection. The stimulation of the vagus nerve is intermittent, and the usual stimulation condition is set to a signal on-time (VNS ON) of 30 s followed by an off-time (VNS OFF) of 3–5 min repeatedly. It has been reported that one third of patients have a >50% reduction in seizure frequency, another one third show a 30%–50% seizure reduction, and the remaining one third show no response. On the other hand, hyperpolarization of neurons, seen on electroencephalograms (EEGs) as positive slow cortical potential (SCP) shifts, represents activation of inhibitory postsynaptic potentials and inhibition of neuronal activity. Production of scalp-recorded positive SCP by a self-regulation training has been used for suppressing seizures, and some patients have even become seizure free. Slow hyperpolarization of cortical pyramidal neurons during the stimulation period in rat models was suggested as an underlying mechanism of action of VNS in suppressing seizures. The aim of this study was to investigate whether VNS induces a positive shift of SCPs in patients with >50% seizure reduction (responders) but not in non-responders.

Methods: This retrospective study was approved by the ethics committees of the Kyoto University Hospital, Kindai University Hospital and Hiroshima University Hospital (IRB#E1736, #25-036 and #Epi1158 respectively). Routine clinical EEGs from 24 patients who were undergoing seizure treatment by VNS were analyzed. The patients were divided into 2 groups by hardware time constant (TC) of EEG: the TC 10-s group (10 patients) and TC 2-s group (14 patients). The SCPs at 5 electrodes (vertex and adjacent ones) were compared between the 2 states of VNS: during stimulation and between stimulations. A positive shift of the SCP was considered to be “present” when it was observed on the 5 electrodes during the stimulation period, and the Wilcoxon test value was <0.05. Seizure reduction was independently judged. Correlation between SCP (positivity or not) and seizure reduction (>50% or not) was estimated.

Results: In the TC 10-s group, the correlation between SCP and seizure reduction was significant ($p < 0.05$) (i.e., both good results in 4 and both negative results in 5). In TC 2-s group, the correlation between SCP and seizure reduction was not significant ($p = 0.209$).

Conclusions: This study compared scalp-recorded SCPs during VNS stimulation period with the inter-stimulation interval respectively from 5 electrodes in patients undergoing VNS therapy. The comparison showed that utilization of EEG with a long TC (10 s) revealed positive SCP shifts during VNS in good responders. A positive shift of SCP recorded by using a TC of 10 s could be a surrogate marker for VNS response.

（論文審査の結果の要旨）

迷走神経刺激療法(Vagus Nerve Stimulation：VNS)は、左迷走神経を電気刺激して発作を抑制する難治てんかんの治療法で、1/3 の患者は 50%以上の発作減少をきたす（反応良好群)。しかし、VNS の導入前に反応良好群の予測は困難である。緩電位（Slow Cortical Potential: SCP）は緩徐な脳波成分で、てんかん発作時などの SCP の陰性と陽性変動は、それぞれ神経細胞群の興奮と抑制活動を示す。申請者は、VNS での反応良好群を抽出するために、VNS に伴う SCP の陽性変動が代替マーカーであるかを明らかにする研究を行った。

VNSの装着手術後、脳波と症状が経年的に観察された24例を後方視的に分析した。患者は脳波記録の時定数10秒と2秒の２群から構成された。VNS刺激中の頭蓋頂５電極に陽性SCPを有意に示した患者群と発作減少の反応良好群間の一致性を検討した。逆に陽性SCP不良群と発作減少不良群間の一致性も検討した。その結果、時定数10秒では陽性SCP群と陽性SCP不良群それぞれは発作減少の有無の一致性に有意な相関があり2秒群にはなかった。以上より時定数10秒の脳波のVNS刺激中の陽性SCP所見から、発作減少の反応良好群を予測できることが示された。

以上の研究は VNS による発作抑制機構と SCP の陽性変動の関連の解明に貢献し、難治てんかんの治療に寄与するところが多い。

したがって、本論文は博士（医学）の学位論文として価値あるものと認める。

なお、本学位授与申請者は、平成 29 年 10 月 2 日に実施された論文内容とそれに関連した試問を受け、合格と認められたものである。

要旨公開可能日：　　年　　月　　日　以降